BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

REMARKS

Prior to this Preliminary Amendment, claims 2 to 14 were pending, with claims 9, 10, 13 and 14 being withdrawn due to a restriction requirement. By the present communication, no claims have been added or deleted and claims 2-4 have been amended to define Applicants' invention with greater particularity. Claim 2 has been amended to be directed to a method of detecting "altered expression of growth differentiation factor-5 (GDF-5) in a subject in need thereof" and to clarify that the anti-GDF-5 antibody binds specifically to an invention GDF-5 polypeptide having an amino acid sequence as set forth in SEQ ID NO: 10 or SEQ ID NO: 13 in a specimen of the subject. Claim 2 is further amended to clarify that binding of the anti-GDF-5 antibody is compared to binding of the antibody to the invention GDF-5 polypeptide in "comparable specimens obtained from normal subjects." Finding of a differential binding between the subject's specimen and control specimens from normal subjects determines the existence of an alteration in expression of the invention GDF-5 polypeptide in the subject. The amendments are supported, for example, at page 15, lines 10-12; page 18, lines 7-14; and by Examples 2 and 3. The amendments are also supported by Figures 2 and 3A, which disclose SEQ ID NO: 10 or SEQ ID NO: 13, respectively. As such, it is submitted that the amendments to claim 2 do not add new matter.

Claim 3 has been amended to recite that "the specimen comprises uterine neoplasm tissue or endometriosis tissue." The amendment is supported, for example, at page 15, lines 12-14, and by the previously entered claim 3. As such, it is submitted that the amendment to claim 3 does not add new matter.

Claim 4 has been amended to recite that "the specimen comprises skeletal tissue." The amendment is supported, for example, at page 15, lines 12-14, and by the previously entered claim 3. As such, it is submitted that the amendment to claim 4 does not add new matter.

Upon entry of the amendments, claims 2-14 will be pending, with claims 9, 10, 13 and 14 being withdrawn.

The Rejection under 35 U.S.C. § 112, First Paragraph

The rejection of claims 2-8, 11 and 12 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, is respectfully traversed.

The Examiner acknowledges that the specification is enabling for a method of detecting GDF-5 comprising the amino acid sequence shown in Figure 2 (Advisory Action, page 2). It is alleged, however, that the specification, while being enabling for a method of detecting the GDF-5 polypeptide comprising the amino acid sequence shown in Figure 2, does not reasonably provide enablement for a method of detecting a cell proliferative disorder by detecting GDF-5. While the Applicants maintain the traversal of this ground of rejection for reasons previously made of record (see, for example, Applicants response mailed May 27, 2003) , the claims have been herein amended in order to expedite prosecution and narrow the issues for appeal. In particular, the currently amended claims are directed to methods of "detecting altered expression of the growth differentiation factor-5 . . . having the amino acid sequence as set forth in SEQ ID NO: 10 or SEQ ID NO: 13", i.e., the amino acid sequences shown in Figure 2.

In view of the amendments, therefore, Applicants submit that the rejection for alleged lack of enablement is overcome and reconsideration and withdrawal of the rejection of claims 2-8, 11 and 12 as allegedly lacking enablement are respectfully requested.

The Rejection under 35 U.S.C.§ 112, Second Paragraph

The rejection of claims 2-8, 11, 12 and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter regarded as the invention is respectfully traversed.

It is alleged in the Office Action that claims 2-8, 11, and 12 are indefinite because it is unclear whether the term "GDF-5", as recited in the terms "growth differentiation factor-5...cell proliferative disorder," "GDF-5 specific antibody," "GDF-5 associated disorder," and "GDF-5 associated cell proliferative disorder," is limited to having an amino acid sequence as set forth in SEQ ID NO: 10 or SEQ ID NO: 13. For the reasons set forth above, the claims have been amended and are directed to methods of "detecting altered expression of growth differentiation

factor-5." As such, the terms "growth differentiation factor-5...cell proliferative disorder," "GDF-5 associated disorder," and "GDF-5 associated cell proliferative disorder" are not found in the currently amended claims and the rejection, therefore, is moot with respect to these terms. Regarding the term "GDF-5 specific antibody", claim 2 has been amended to more clearly indicate that an antibody useful in a method of the invention is one that "specifically binds a GDF-5 polypeptide having an amino acid sequence as set forth in SEQ ID NO: 10 or SEQ ID NO: 13." Further references to GDF-5 have been amended to recite "the GDF-5 polypeptide". As such, Applicants submit that the subject matter of amended claim 2 (and claims 3-8, 11, and 12 dependent thereon) is clearly defined. Therefore, Applicants respectfully request that this ground of the rejection be reconsidered and withdrawn.

The Examiner also asserts that claim 14 is indefinite because the term "modified cellulose" is not defined and, therefore, the limitations of the element cannot be determined. Claim 14 is withdrawn from prosecution. However, to be responsive to the Examiner, Applicants maintain the traversal of this rejection and submit that one skilled in the art, in view of the nature of the claimed subject matter (i.e., an immunologic method for detecting a protein), the specification (e.g., page 15, line 18, to page 16, line 10, describing such immunoassays), and the plain meaning of the term, would know the metes and bounds of modified cellulose useful for the claimed methods. In this regard, Applicants submit that is well known that cellulose is a chemically inert, straight chained polysaccharide composed of linked glucose subunits, with physical properties suitable for binding proteins, such as antibodies. It is further submitted that one skilled in the art would understand that "modified cellulose" as used in claim 14 includes a cellulose polysaccharide, obtained from natural sources or synthesized, that has been physically or chemically modified to affect its protein binding properties, as exemplified, for example, in Exhibit A. Furthermore, examples of cellulose products that have been physically and/or chemically modified and are useful in an immunologic method for detecting a protein are vast and well known in the art (see, for example, Exhibit B; see also, Applicants response mailed May 27, 2003). In fact, one such well known modified cellulose, nitrocellulose, is disclosed in

the current specification (see, for example, page 24, lines 13-16). As such, it is submitted that, based on the plain meaning of the term, the current specification, and the knowledge in the art, a skilled artisan would know that the modification of a cellulose intended by the term "modified" includes physical and/or chemical modification that affects the protein binding properties of the cellulose, as compared to natural cellulose. Accordingly, it is maintained that one skilled in the art would readily understand the metes and bounds of the term "modified cellulose" as the term is used in claim 14. Applicants therefore respectfully request reconsideration and withdrawal of the rejection as it pertains to the term "modified cellulose" as used in claim 14.

The Examiner also asserts that the term "normal cell" as used in claims 2-8, 11, 12, and 14 is indefinite because the term is not defined in the specification or in the claims. It is initially noted that claim 2 has been amended to remove the term "normal cell" and instead require comparison of binding of the GDF-5 specific antibody to patient specimen and to "*comparable specimens obtained from normal subjects.*" In order to be fully responsive to the Office Action, Applicants will address the rejection as applied to the currently amended claims.

The Examiner bases the rejection on the belief that the term "normal" is relative and, therefore, indefinite. It is submitted, however, that the mere fact that a term is relative is not dispositive as to its clarity, particularly as the term "normal" is used in amended claim 2, in which the term is used together with the term "altered expression." In addition, Applicants submit that the plain meaning of the term "normal" is derived from the well known concept of the statistical norm, which would vary according to the type of specimens being compared.

Applicants further point out that the specification discloses "normal" expression patterns of the invention GDF-5 polypeptide in a variety of adult tissues (Example 2) as well as in embryonic tissues (Examples 2 and 3). As such, one skilled in the art would recognize that expression of the invention GDF-5 polypeptide in a patient sample (i.e., one suspected of altered expression of the test polypeptide) should be compared with the level of expression in a comparable control tissue specimen, such as specimens from "normal" subjects, for example, adult uterine tissue or placenta, brain, thymus, lung, kidney, and adrenal gland, or, in embryos,

skeletal tissue. Thus, if the subject's specimen is adult uterine tissue or placenta, "a comparable specimen obtained from normal subjects" would be uterine tissue or placenta representative of "normal" (i.e., healthy) individuals. To assume that "normal

In view of the teachings in the specification, numerous examples of the type of specimens that could be expected to have normal expression of the invention GDF-5 peptide in healthy adult and embryonic tissues would be apparent to the skilled artisan or could readily be ascertained using the teachings in the specification, such that the metes and bounds of the claimed subject matter clearly would be known. Therefore, Applicants submit that those of skill in the art, reading the claims, would know the metes and bounds of the claimed subject matter. Accordingly, it is respectfully requested that the rejections of claims 2-8, 11, 12, and 14 under 35 U.S.C. § 112, second paragraph, be withdrawn.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Respectfully submitted,

Dated: January 30, 2004

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

USPTO Customer Number 28213
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

Enclosures: Exhibits A and B

1: Biotechnol Adv. 2002 Nov;20(3-4):191-213. Related Articles, Link

Cellulose-binding domains. Biotechnological applications.

Levy I, Shoseyov O.

The Institute of Plant Science and Genetics in Agriculture and The Otto Warburg Centre for Agricultural Biotechnology, The Faculty of Agricultural Food and Environmental Quality Sciences, The Hebrew University of Jerusalem, PO Box 12, Rehovot 76100, Israel

Many researchers have acknowledged the fact that there exists an immense potential for the application of the cellulose-binding domains (CBDs) in the field of biotechnology. This becomes apparent when the phrase "cellulose-binding domain" is used as the key word for a computerized patent search; more then 150 hits are retrieved. Cellulose is an ideal matrix for large-scale affinity purification procedures. This chemically inert matrix has excellent physical properties as well as low affinity for nonspecific protein binding. It is available in a diverse range of forms and sizes, is pharmaceutically safe, and relatively inexpensive. Present studies into the application of CBDs in industry have established that they can be applied in the modification of physical and chemical properties of composite materials and the developmen of modified materials with improved properties. In agro-biotechnology, CBDs can be used to modify polysaccharide materials both in vivo and in vitro. The CBDs exert nonhydrolytic fiber disruption on cellulose-containing materials. The potential applications of "CBD technology" range from modulating the architecture of individual cells to the modification of an entir organism. Expressing these genes under specific promoters and using appropriate trafficking signals, can be used to alter the nutritional value and texture of agricultural crops and their final products.

PMID: 14550028 [PubMed - as supplied by publisher]

Exhibit A

Oct 29 2003 06:52::

Short Contents | Full Contents Other books @ NCBI

Molecular Biology of the Cell, 3rd edn. Part I. Introduction to the Cell Chapter 4. How Cells Are Studied Fractionation of Cells and Analysis of Their Molecules 20

Figure 4-39. Three types of matrices used for chromatography. In ion-exchange chromatography (A) the insoluble matrix carries ionic charges that retard molecules of opposite charge. Matrices commonly used for separating proteins are diethylaminoethylcellulose (DEAE-cellulose), which is positively charged, and carboxymethylcellulose (CM-cellulose) and phosphocellulose, which are negatively charged. The strength of the association between the dissolved molecules and the ion-exchange matrix depends on both the ionic strength and the pH of the solution that is passing down the column, which may therefore be varied in a systematic fashion (as in Figure 4-40) to achieve an effective separation. In gel-filtration chromatography (B) the matrix is inert but porous. Molecules that are small enough to penetrate into the matrix are thereby delayed and travel more slowly through the column. Beads of cross-linked polysaccharide (dextran or agarose) are available commercially in a wide range of pore sizes, making them suitable for the fractionation of molecules of various molecular weights, from less than 500 to more than 5 x 10^6. Affinity chromatography (C) utilizes an insoluble matrix that is covalently linked to a specific ligand, such as an antibody molecule or an enzyme substrate, that will bind a specific protein. Enzyme molecules that bind to immobilized substrates on such columns can be eluted with a concentrated solution of the free form of the substrate molecule, while molecules that bind to immobilized antibodies can be eluted by dissociating the antibody-antigen complex with concentrated salt solutions or solutions of high or low pH. High degrees of purification are often achieved in a single pass through an affinity column.

Navigation

About this book

I. Introduction to the Cell

4. How Cells Are Studied

Introduction

Looking at the Structure of Cells in the Microscope

Isolating Cells and Growing Them in Culture

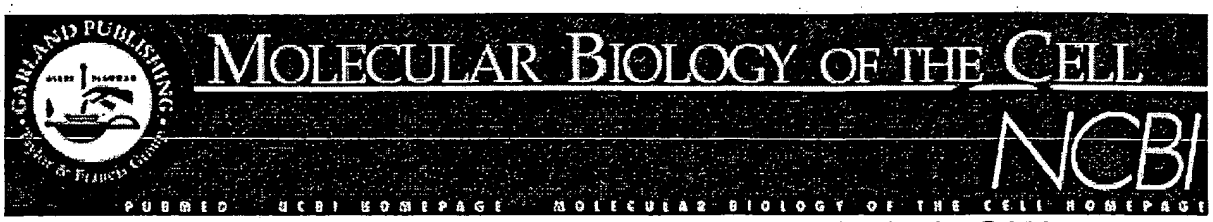
Fractionation of Cells and Analysis of Their Molecules

Tracing and Assaying Molecules Inside Cells

References

Search

This book All books PubMed



Short Contents | Full Contents Other books @ NCBI

Navigation

About this book

I. Introduction to the Cell

4. How Cells Are Studied

Introduction

Looking at the Structure of Cells in the Microscope

Isolating Cells and Growing Them in Culture

Fractionation of Cells and Analysis of Their Molecules

Tracing and Assaying Molecules Inside Cells

References

Search

Go

This book All books

PubMed

Exhibit B

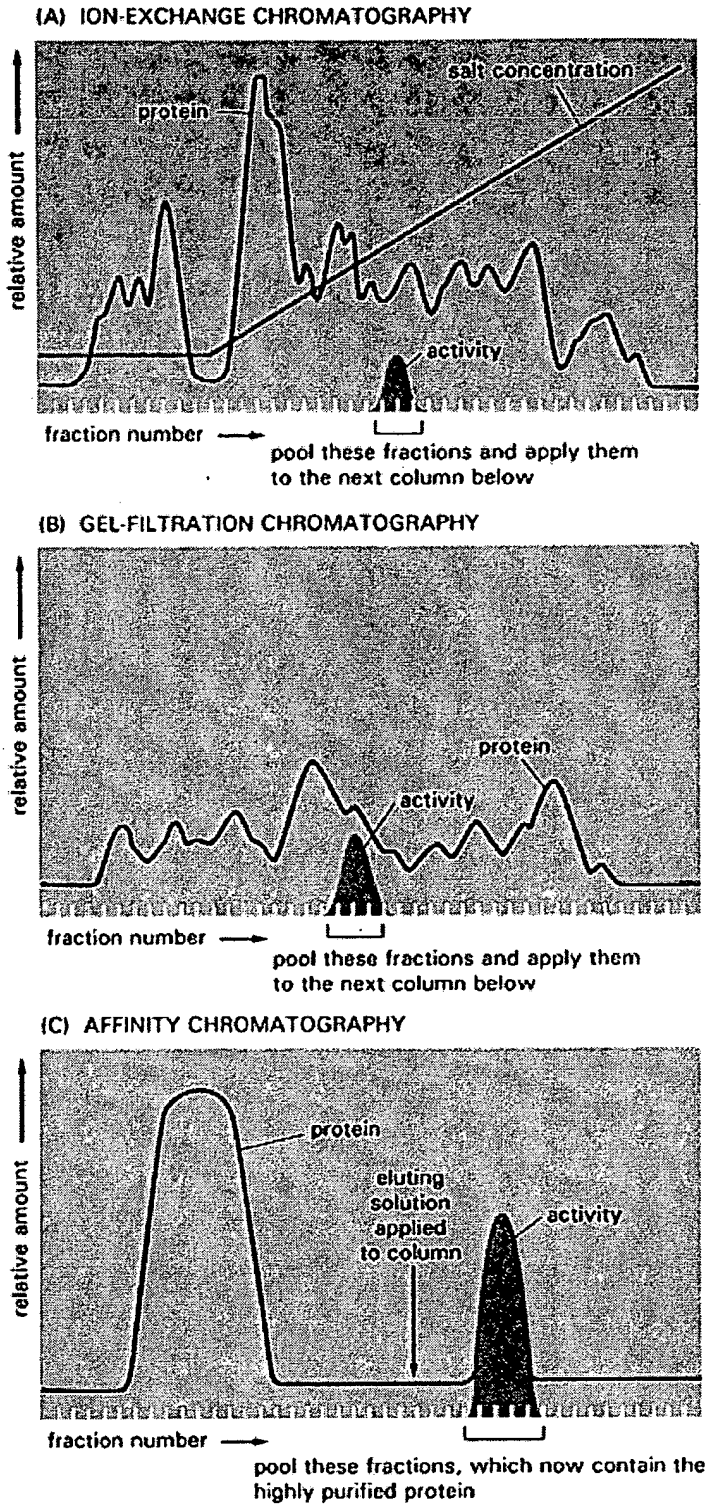


Figure 4-40. Protein purification by chromatography. Typical results obtained when three different chromatographic steps are used in succession to purify a protein. In this example a homogenate of cells was first fractionated by allowing it to percolate through an ion-exchange resin packed into a column (A). The column was washed, and the bound proteins were then eluted by passing a solution containing a gradually increasing concentration of salt onto the top of the column. Proteins with

the lowest affinity for the ion-exchange resin passed directly through the column and were collected in the earliest fractions eluted from the bottom of the column. The remaining proteins were eluted in sequence according to their affinity for the resinthose proteins binding most tightly to the resin requiring the highest concentration of salt to remove them. The protein of interest eluted in a narrow peak and was detected by its enzymatic activity. The fractions with activity were pooled and then applied to a second, gel-filtration column (B). The elution position of the still-impure protein was again determined by its enzymatic activity and the active fractions pooled and purified to homogeneity on an affinity column (C) that contained an immobilized substrate of the enzyme.